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Effects of Weightlessness on Human Fluid and Electrolyte Physiology

CAROLYN S. LEACH AND PHILIP C. JOHNSON, JR.

Introduction

The fluid-regulating systems of the body have been of interest to space medicine researchers since results from the earliest flights indicated significant changes in this area (Berry et al. 1966; Dietlein and Harris 1966; Lutwak et al. 1969). The virtual absence of gravity causes a decrease in posturally induced hydrostatic force in the extremities, which leads to cephalad redistribution of blood. This redistribution is thought to be responsible for most of the spaceflight-induced changes in fluid and electrolyte metabolism. Plasma volume decreases (Johnson 1979) and water and electrolyte balances become negative (Leach 1979) in space travelers. In addition to these clear-cut effects, more complex and subtle changes in renal and circulatory dynamics, endocrine function, body biochemistry, and metabolism occur during spaceflight.

Two Phases of the Adaptation Process

Studies in which weightlessness is simulated by decreasing lower-extremity hydrostatic forces (as by bed rest or water immersion) have indicated the presence of at least two phases in the adaptation of the fluid and electrolyte homeostatic systems to microgravity (Leach et al. 1983). The "acute" phase is believed to occur within a few hours of attaining weightlessness. Since it has been difficult for astronauts to perform experiments early in a flight, most of the evidence for existence of this phase has come from simulation studies. Bed-rest studies (Leach et al. 1983; Nixon et al. 1979) have shown that central venous pressure (CVP) increases as early as 5 min after bed rest begins (Nixon et al. 1979). This is followed by an increase in the size of the left ventricle, but there is no change in cardiac output or arterial pressures (Nixon et al. 1979). The increased CVP is thought to be interpreted physiologically as an increase in total blood volume. Glomerular filtration rate (GFR) decreases by about 2 hr and effective renal plasma flow (ERPF) by 4 hr, but both return to pre-bed-rest levels by 8 hr. Plasma aldosterone and antidiuretic

hormone (ADH) decrease between 1 and 6 hr after the beginning of bed rest (Leach et al. 1983; Nixon et al. 1979).

The transient acute phase, found in simulation studies and confirmed by recent Spacelab data to be discussed below, leads to a later "adaptive" phase. Evidence for the existence of the adaptive phase has come from blood and urine samples taken in-flight during Gemini, Apollo, Skylab, and Spacelab missions.

Early Spaceflight Findings

Data from limited in-flight samples, along with preflight and postflight measurements of many physiological parameters, provided evidence that mass is lost, water balance becomes negative, electrolytes and certain minerals are depleted, and cardiovascular deconditioning occurs as a result of weightlessness (Berry et al. 1966; Hoffler 1977; Leach et al. 1975). Fluid, potassium, and nitrogenous compounds were apparently lost from cells as well as from blood (Leach et al. 1975). Levels of some of the hormones involved in regulating fluid and electrolyte balance were altered; for example, urinary ADH and aldosterone and plasma angiotensin were increased postflight. Plasma volume and red cell mass decreased, and orthostatic tolerance and exercise capacity were reduced (Hoffler and Johnson 1975).

Skylab

Experiments for Skylab were planned to document the time course of known physiological changes and to measure additional parameters during long flights. Intake of fluid and nutrients during flight was carefully monitored.

The first in-flight measurements of body mass were performed on Skylab (Thornton and Ord 1977). The crew members lost an average of 2.8 kg, 3.8% of preflight body mass, during flight (Leach and Rambaut 1977). About half the loss of body mass occurred during the first 2 days of flight, with the rest of the loss being more gradual but continuing throughout the missions. Depletion of water was thought to be responsible for the rapid phase of mass loss and depletion of fat and protein for the slow phase (Leach and Rambaut 1977).

Increased urinary excretion of water was expected to account for the water deficit. Surprisingly, urinary excretion decreased during the first 10 days of the missions, and free water clearance decreased slightly (Leach and Rambaut 1977). Water balance studies showed that the main cause of the net body water reduction during the first 2 days of flight was a decrease in fluid intake.

To investigate the postulated shift of fluid away from the lower extremities, the leg volume of Skylab crew members was measured by plethysmography (Thornton et al. 1977). It was estimated that in the first few days of flight, 1.8 l of fluid disappeared from the legs (Hoffler 1977), an amount considerably greater than the 600 to 800 ml redistributed by a change in body position (upright to supine or vice versa) (Sjöstrand 1953). The amount of fluid lost from the legs was almost equal to the total body fluid decrement.

The loss of so much body fluid implies that levels of other blood and tissue components are reduced also. Plasma osmolality and levels of sodium and chloride were decreased during flight, and the amounts of sodium, potassium, calcium, phosphate, and magnesium were increased in 24-hr urine pools collected in-flight. Leach and Rambaut (1977) calculated that approximately 100 meq of sodium were lost from the extracellular space. Electrolytes and other cell constituents may have been translocated from cells to blood. Plasma levels of potassium, calcium, and phosphate increased during flight.

Plasma angiotensin and urinary aldosterone and cortisol were increased over their preflight levels during the whole flight but were particularly increased at the beginning of each flight (Leach and Rambaut 1977). These hormones are released in response to stress and to changes in plasma osmolality and electrolytes. Increased angiotensin and aldosterone may have caused at least part of the increased urinary excretion of potassium, but it is unusual for high levels of aldosterone to be associated with increased sodium excretion. Urinary excretion of antidiuretic hormone (ADH) was decreased during flight, another unexpected finding because the loss of fluid would normally stimulate ADH secretion, and hyponatremia persisted in spite of the apparent reduction in ADH.

Renal function was not measured directly during the Skylab flights. Slight increases in creatinine clearance (Leach 1981), decreased urinary and plasma uric acid, and increased plasma angiotensin indicated that renal function may be affected by weightlessness.

Recent Findings from the Space Shuttle

Several experiments involving fluid and electrolyte physiology have now been performed aboard the space shuttle. Venous pressure was measured for the first time on *Spacelab 1*, 22 hr after launch (Kirsch et al. 1984). At that time venous pressure was lower than it was on the day before launch. Measurement of central and peripheral venous pressures 1 and 12 hr after landing indicated that fluid redistribution after reexposure to gravity was completed between these times. If redistribution caused by microgravity takes about the same amount of time, it is probably complete before 22 hr.

Studies of body fluid changes during spaceflight have been hampered by lack of knowledge about changes in circadian rhythm and by flight-related

problems such as space adaptation syndrome or crew members being on different work/rest cycles or being unable to draw blood very soon after reaching orbit or at the same time each day.

In one experiment a mission specialist collected his urine as pools representing 5 to 26 hr, and the excretion rates of electrolytes and selected hormones were determined. The earliest change detected in this study was a transient increase in the excretion rate of ADH in the first in-flight sample. This was closely followed by a transient increase in the excretion rate of cortisol. Sodium excretion decreased on the day after the peak in cortisol excretion occurred, but later in the flight it increased. Potassium excretion increased at the same time as cortisol excretion on the first day of flight, with smaller peaks on later flight days. Some of these changes may have been caused or affected by the presence of space adaptation syndrome. On the sixth and last day of the flight, aldosterone excretion rate tripled, and cortisol and ADH excretion rates increased by lesser amounts. The excretion rates of fluid, potassium, chloride, calcium, and magnesium increased at the same time. The loss of sodium, which might be expected to result in increased aldosterone secretion, was no greater late in the flight than it had been during the preflight period.

On the Spacelab flights, blood samples were drawn 22 or more hours after launch. Aldosterone, cortisol, and ADH were measured in blood samples from Spacelab 1 by Dr. K.A. Kirsch (personal communication), and our laboratory has measured these and other hormones as well as serum osmolality, sodium, and potassium in other Spacelab experiments. The four crew members on Spacelab 1 who participated in experiments were on two different work/rest cycles, but their blood samples were taken at the same clock time, and studies of the circadian rhythms of several urinary variables showed that the circadian rhythm of metabolic functions did not change (Leach, Johnson, & Cintrón 1985). Blood samples were obtained from four mission and payload specialists on Spacelab 2 and two mission specialists on Spacelab 3. The crew members on Spacelab 2 were on two different work/rest cycles, and during flight they collected blood samples during the postsleep activity period. This was 6:30 or 7:00 a.m. Houston time for two crew members and 5:00 or 6:00 p.m. for the other two. Because of differences in sample collection times, one must be cautious in interpreting the results, but the small number of subjects and time points in any one experiment makes it desirable to examine the results of these three experiments together.

The combined results for all three Spacelab studies (Leach et al. 1985) showed that hyponatremia developed within 20 hr after the onset of weightlessness and continued throughout the flights, and hypokalemia developed by 40 hr. Serum potassium returned to preflight levels later and then increased. Serum chloride was decreased on most in-flight days on which it was measured, but it immediately returned to preflight levels on landing day.

Antidiuretic hormone, which increased transiently in urine in the

shuttle experiment described above and decreased in urine during Skylab flights (Leach and Rambaut 1977) and in plasma during bed rest (Nixon et al. 1979), was increased in plasma throughout the Spacelab flights. Aldosterone decreased by 40 hr, but after 7 days it had reached preflight levels. Angiotensin I was elevated after 2 days in flight. Cortisol increased early but decreased later in the flight. Adrenocorticotrophic hormone was increased until the seventh day, when levels of cortisol and aldosterone returned to or surpassed baseline.

Current Problems

The changes that occur in human fluid and electrolyte physiology during the acute and adaptive phases of adaptation to spaceflight are summarized in Tables 11.1 and 11.2. A number of questions remain to be answered.

At a time when plasma volume and extracellular fluid volume are contracted and salt and water intake is unrestricted, ADH does not correct the volume deficit and serum sodium decreases. Change in secretion or activity of a natriuretic factor during spaceflight is one possible explanation.

Recent identification of a polypeptide hormone produced in cardiac muscle cells which is natriuretic, is hypotensive, and has an inhibitory effect on renin and aldosterone secretion (Atarashi et al. 1984; Palluk et al. 1985) has renewed interest in the role of a natriuretic factor. The role of this atrial natriuretic factor (ANF) in both long- and short-term variation in extracellular volumes and in the inability of the kidney to bring about an escape from the sodium-retaining state accompanying chronic cardiac dysfunction makes it reasonable to look for a role of ANF in the regulation of sodium during exposure to microgravity. Prostaglandin E is another hormone that may antagonize the action of ADH (Anderson et al. 1976). Assays of these hormones will be performed on samples from crew members in the future.

TABLE 11.1. Acute phase of actual or simulated microgravity effects on fluid and electrolyte physiology

Cardiovascular effects (bed rest)
Increased central venous pressure
Increased size of left ventricle
Renal effects (bed rest)
Decreased GFR
Decreased ERPF
Endocrine system changes (Spacelab)
Increased plasma cortisol
Decreased plasma angiotensin I

TABLE 11.2. Adaptive phase of microgravity effects on fluid and electrolyte physiology, compared with preflight.

Mass loss
Water
Protein
Fat
Changes in fluid volumes in major body compartments
Decrease in lower body
Increase in upper body
Decrease in intracellular water
Decrease in extracellular fluid
Negative fluid balance
Decreased fluid intake
Increased evaporative water loss
Decreased renal excretion of water
Slightly decreased free water clearance
Decreased total body water
Electrolyte balance
Decreased exchangeable body potassium
Decreased sodium in extracellular space
Increased excretion of sodium
Increased excretion of potassium
Blood levels of electrolytes
Increased potassium
Decreased sodium
Decreased chloride
Decreased osmolality
Endocrine system changes
Increased plasma angiotensin I
Increased urinary aldosterone
Increased urinary cortisol
Increased plasma ADH
Decreased urinary ADH
Renal function
Decreased plasma and urinary uric acid
Increased creatinine clearance

Cardiovascular intolerance to standing, found to occur immediately after landing in many astronauts, is thought to be related to loss of fluid and electrolytes during weightlessness. In the space shuttle, reentry acceleration is experienced in the head-to-foot direction because the crew members are sitting upright. The gravitational force in that direction is usually about 1.2 times the normal 1.0 *G* (Nicogossian and Parker 1982). The rapid increase in accleration forces during reentry would be expected to pull body fluids toward the legs. If there has been substantial loss of body fluid, fluid volume in the upper part of the body may decrease enough to cause cardiovascular symptoms. Some of these symptoms might be alleviated if fluid and electrolyte metabolism were fully re-

adapted to earth's gravity before landing. Attempts have been made, with some success, by investigators in the United States and Soviet space programs to prevent or ameliorate orthostatic intolerance.

One method that has been used to counter the orthostatic intolerance is fluid and electrolyte loading. If fluid and electrolytes are replaced, blood volume should begin to increase and blood pressure should approach preflight levels. This should be done before exposure to the increased acceleration during the deorbit period. It is now standard practice for U.S. astronauts to consume the equivalent of a liter of physiological saline solution in the form of water and salt tablets before landing is initiated. This practice has been shown to be effective in reducing the severity of symptoms of cardiovascular deconditioning (Bungo et al. 1985). Similar countermeasures have been used by cosmonauts on Soyuz missions (Grigoriev 1983).

Another approach to prevention of postflight orthostatic intolerance is the use of lower-body negative pressure (LBNP) during flight to bring more fluid into the legs; this has been used with some success in the Soviet space program (Grigoriev 1983).

There is now considerable indirect evidence that renal function is altered during weightlessness (Leach, Johnson, & Cintrón 1985), but direct measurements of renal function have been done only in bed-rest studies. Renal function tests will be performed in conjunction with measurement of hormones, electrolytes, plasma volume, and other factors on Spacelab missions in the future. Intake of food and water will be measured throughout the mission, and urine will be collected void by void. Blood samples will be taken at intervals, beginning at 3 hr after launch, and the first renal function test will start at 3.5 hr. A catheter to measure central venous pressure will be inserted before launch and removed 12 hr into the flight. Plasma volume and extracellular fluid will be measured on the second and sixth days of flight. These integrated experiments are expected to provide information important for understanding what happens in both phases of the fluid and electrolyte response to weightlessness.

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THE ENDOCRINE SYSTEM IN SPACE FLIGHT†

C. S. LEACH, P. C. JOHNSON and N. M. CINTRON
NASA/Johnson Space Center, Biomedical Laboratories, Mail Code SD4, Houston, TX 77058, U.S.A.

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Abstract—Hormones are important effectors of the body's response to microgravity in the areas of fluid and electrolyte metabolism, erythropoiesis, and calcium metabolism. For many years antidiuretic hormone, cortisol and aldosterone have been considered the hormones most important for regulation of body fluid volume and blood levels of electrolytes, but they cannot account totally for losses of fluid and electrolytes during space flight. We have now measured atrial natriuretic factor (ANF), a hormone recently shown to regulate sodium and water excretion, in blood specimens obtained during flight. After 30 or 42 h of weightlessness, mean ANF was elevated. After 175 or 180 h, ANF had decreased by 59%, and it changed little between that time and soon after landing. There is probably an increase in ANF early inflight associated with the fluid shift, followed by a compensatory decrease in blood volume. Increased renal blood flow may cause the later ANF decrease. Erythropoietin (Ep), a hormone involved in the control of red blood cell production, was measured in blood samples taken during the first Spacelab mission and was significantly decreased on the second day of flight, suggesting also an increase in renal blood flow. Spacelab-2 investigators report that the active vitamin D metabolite 1α, 25-dihydroxyvitamin D_3 increased early in the flight, indicating that a stimulus for increased bone resorption occurs by 30 h after launch.

1. INTRODUCTION

Recent evidence suggests that the physiologic responses to space flight begin immediately. On the basis of weightlessness simulation studies[31] and findings that leg volume decreases and the face becomes puffy inflight[36], it has been proposed that the removal of the gravitational force on the legs results in an early and transient increase in central blood volume. On the Space Shuttle such a fluid redistribution may begin even before weightlessness is achieved. The launch configuration causes Space Shuttle crewmembers to recline for several hours before launch, and during ascent to orbit, the Shuttle acceleration angle produces $-g_z$ forces on the crew in their seats. Evidence from the D-1 Spacelab mission on the Space Shuttle indicates that fluid redistribution does begin before launch: central venous pressure, when measured beginning 20 min after launch, never exceeded preflight measurements[18]. By the end of the first 24 h of flight, changes have occurred in many physiological systems, especially those related to the distribution of fluid in the body. In most systems, these changes are relatively rapid and a new steady state seems to have been reached.

Because of the importance of the endocrine system in regulation of the body's homeostatic mechanisms, a number of hormones have been studied in the blood and urine of crewmembers during and after space flight. Hormones involved in maintenance of body fluid compartments, erythropoiesis, mineral physiology, and regulation of metabolism have had primary focus in the U.S. manned space flight program.

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2. FLUID AND ELECTROLYTE REGULATION

Early studies showing loss of weight[14] and a decrease in blood volume and interstitial volume of the lower extremities[15] after space flight indicated that a loss of body fluid occurred during flight. The translocation of fluid from the extremities to the head and chest during space flight is thought to cause a transient increase in central blood volume and central venous pressure. The results of Kirsch *et al.*[18] suggest this is complete prior to the first inflight measurement, while the echocardiographic data of Pourcelot *et al.*[32] and Bungo *et al.*[4] indicate it takes less than 6 h. The increase in central venous pressure is detected by stretch receptors in the heart and superior vena cava and interpreted as an increase in total blood volume. A compensatory loss of water and sodium results. Further investigation has revealed other effects of space flight on fluid physiology and some of the control mechanisms that mediate those effects.

Body composition of the Skylab astronauts was studied in detail before, during and after flight[28]. Water accounted for about half of the weight lost during flight. Although urinary excretion of fluid did not increase, fluid intake decreased to cause a negative water balance[26]. Urinary sodium, potassium, and chloride generally increase in microgravity, with a concomitant increase in urine osmolality, while serum osmolality and sodium are decreased throughout flight[23,26]. In Skylab crewmembers, plasma potassium was slightly increased during most of the

time inflight, but in Spacelab crewmembers, serum potassium was reduced for several days between 30 and 120 h after launch. The maintenance of serum hypo-osmolality and hyponatremia along with increased sodium excretion is surprising because normally these conditions would be corrected by homeostatic regulatory mechanisms including hormones.

Several hormones are known to participate in regulation of body fluid volume and blood levels of electrolytes. For many years antidiuretic hormone (ADH), cortisol, and aldosterone have been considered the most important hormones performing these functions. However, measurements of these compounds in inflight specimens have indicated that their levels cannot account for the entire measured losses of fluid and electrolytes.

Recent Spacelab experiments have shown that ADH increased in plasma during flight[23], but urinary ADH decreased in most Skylab crewmembers relative to preflight levels[26], raising the possibility that the low serum osmolality might have another cause. A transient increase in urinary ADH on the Shuttle[20] may have resulted from symptoms of space motion sickness in the one crewmember whose urine was collected. Space motion sickness, which affects most of the crewmembers, is a confounding variable in the analysis of data resulting from samples obtained during the first 2 days of a flight.

The levels of aldosterone and angiotensin I in inflight samples were particularly inconsistent. Plasma aldosterone did not change significantly during the Skylab flights[26], but in Spacelab astronauts it decreased[23]. Urinary aldosterone, on the other hand, increased in both Skylab[26] and Shuttle astronauts, suggesting increased clearance of the hormone. Angiotensin I, a hormone that stimulates aldosterone production, increased early during Skylab flights, then returned to preflight levels and continued to decrease for several weeks[26]. On Spacelab missions, plasma angiotensin I was reduced for 2 days and then increased[23].

Plasma and urinary cortisol were increased over preflight levels throughout the Skylab flights[26], but on the Space Shuttle both were elevated for a few days, then decreased to preflight levels or below[20,23]. Cortisol may be particularly important because it has been implicated as a cause of bone calcium loss in humans; this will be discussed further in another section. Adrenocorticotropin decreased at various times during Skylab flights[17], but on the Spacelabs it was increased for at least a week[23].

Additional variables must be measured before the picture of fluid regulation in space can be completed. Low serum potassium and the persistence of lower serum sodium during flight cannot be explained in terms of observed angiotensin I, ADH, cortisol, and aldosterone levels. The electrolyte data might be partially explained by increased activity of a natriuretic factor during flight or by an increase in renal blood flow. Renal blood flow has not yet been measured during flight. Since atrial natriuretic factor (ANF) has now been recognized as a hormone that regulates sodium and water excretion, we have measured ANF in blood specimens obtained during and after the Spacelab-2 mission.

Blood samples were collected from 4 astronauts on this mission on 3 days preflight, 2 days inflight, and 3 days postflight. The first time it was measured after launch, 30 or 42 h into the flight, ANF increased 36% over the preflight mean (Fig. 1). After 175 or 185 h of weightlessness, ANF had decreased by 59%, and

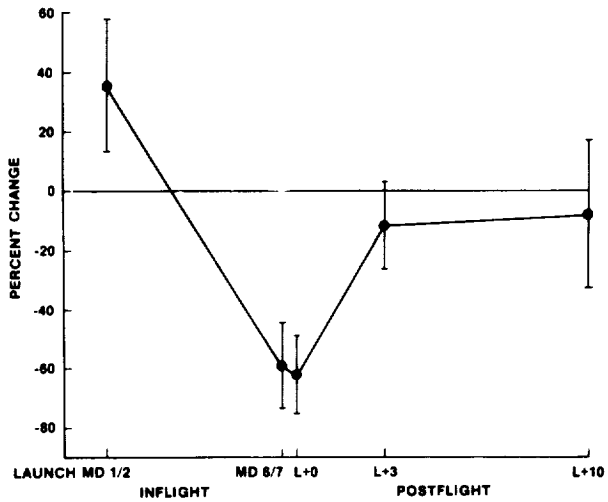

Fig. 1. Mean percent change in plasma ANF during and after the Spacelab 2 mission. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA), and plasma and red cells were separated before freezing. Plasma samples for ANF assay were extracted with a Sep-Pak C18 cartridge[35]. Atrial natriuretic factor was determined by radioimmunoassay[12]. For each of 4 crewmembers, each measurement was compared to the mean for 3 preflight days. Bars represent standard error.

it changed little between that time and immediately (1.5 h) after landing. Three days after landing, plasma ANF had increased to preflight level in all crewmembers.

Although urine data are not available for this flight, a number of other variables were measured in blood samples. Sodium had decreased about 1% late in the flight, but was at preflight level immediately after landing. Potassium, on the other hand, increased 9% after 175-185 h of weightlessness, then decreased slightly after landing. Plasma osmolality did not follow the pattern of either of these electrolytes: it decreased during flight, particularly on the earlier day (4%). Osmolality returned to preflight level at landing. The ingestion of a liter of water and eight salt tablets several hours before landing, used as a countermeasure against orthostatic intolerance, occurred after the later inflight blood collection but probably influenced levels of electrolytes and hormones in samples taken on landing day.

Several other hormones were measured in plasma samples from Spacelab 2 crewmembers. Angiotensin I decreased by 40% at the early inflight sampling time, but by the later sampling time it had increased by 40%. It increased even more at landing, then decreased during the recovery period. Aldosterone had a similar pattern of change, but it decreased only about 10% early in the flight and was at preflight level late in the flight while angiotensin I was elevated. Cortisol was increased over preflight levels at all times during and after the flight, especially on the second mission day and immediately after landing. Even 10 days after landing, cortisol was 50% higher than it had been before flight, and the increase was highly consistent in all four crewmembers. This pattern was more similar to that of Skylab crewmembers than to cortisol measurements from other Spacelab missions[23,26]. Adrenocorticotropin, the pituitary hormone that stimulates secretion of cortisol, increased similarly but generally not as much as cortisol.

An increase in plasma ANF has been observed in weightlessness simulation experiments[10], with a maximum at 30 minutes after the beginning of headdown bedrest. These results indicate that 30 h after launch is too late to measure the highest levels of plasma ANF during actual weightlessness. As discussed above, fluid redistribution in Shuttle crewmembers may occur before launch. Release of ANF in humans can be caused by increased blood volume[38] a condition that would be sensed for a short time when fluid shifts to the head and chest. An increase in atrial pressure, which would result from increased blood volume, is thought to stimulate ANF release[13]. Measurement of the left atrium of astronauts by echocardiography indicates that atrial size increases very early during flight but decreases later and returns to normal after landing (Dr. John Charles, personal communication). Atrial pressure has not yet been measured during weightless, but increased atrial dimensions indicate that atrial pressure may be increased. Another possible cause of ANF increase is suggested by the finding that ADH, which was found at increased levels in blood plasma of astronauts on Spacelabs 1 and 3, can stimulate release of ANF in the rat [29]

After 6 or 7 days of weightlessness, adaptation of most physiological systems has occurred; red cell mass, plasma volume [22], and atrial pressure are probably reduced.

Although crewmembers ingest a liter of physiological saline before landing and the return to Earth's gravity might be expected to affect cardiovascular variables, echocardiographic studies show that atrial dimensions are decreased just after landing (Dr John Charles, personal communication), so that decreased ANF might be expected. Blood volume does not fully recover for at least 2 weeks, and restoration of preflight vascular tone may not occur immediately because distension of the veins may result from low venous pressure.

Atrial natriuretic factor promotes excretion of sodium and water [33] and inhibits secretion of renin[5] and aldosterone[2]. Early release of excessive amounts of ANF may explain natriuresis early in flight, but the continued loss of sodium apparently cannot be explained by ANF, since circulating ANF decreases later. Higher levels of ANF would probably exacerbate the hyponatremia that begins after a day or more of flight. It is possible that the decreased

ANF contributes to an increased level of angiotensin I at 175-185 h. Although the aldosteone level at that time does not reflect the increase in angiotensin, it is possible that aldosterone production is increased or unchanged and it is being excreted at an elevated rate as observed in Skylab astronauts.

The action of still other hormones may help to explain changes in fluid and electrolyte metabolism during space flight. Prostaglandin E antagonizes the action of ADH[1] and will be measured during space flight and bedrest. There is evidence that circulating prostaglandin levels are influenced by body position: prostaglandin #2 increased in renal venous blood when subjects sat up after being supine[16]. Prostaglandins may also be involved in bone mineral metabolism.

The changes in fluid and electrolyte metabolism in space flight indicate that weightlessness may affect kidney function. Because of the invasiveness of standard techniques for measuring such variables as renal blood flow and glomerular filtration rate (GFR), these variables have not yet been measured in space. However, our laboratory has measured GFR and effective renal plasma flow (ERPF) during headdown bedrest, and ERPF had decreased 26% after 4 h[25]. Eight hours after bedrest began, both variables had increased to pre-bedrest levels or higher. Creatinine clearance studies performed during the Skylab flights indicated that creatinine clearance and therefore GFR increases slightly[19].

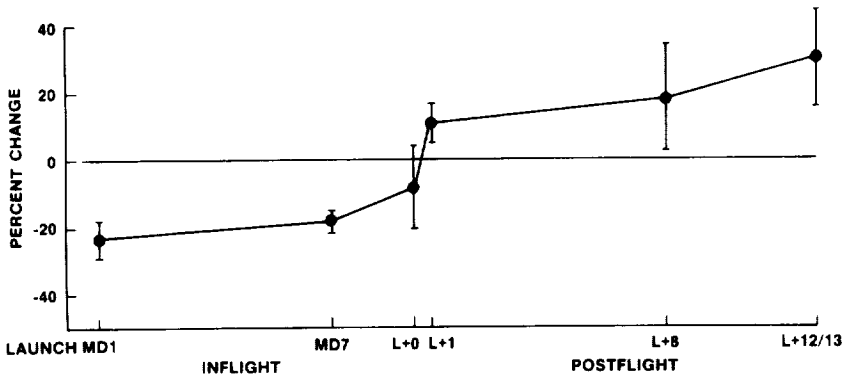

Fig. 2. Mean percent change in plasma erythropoietin during and after the Spacelab 1 mission. For each of 4 crewmembers, each measurement was compared to the mean for 3 flight days. Bars represent standard error.

If increased renal blood flow were characteristic of physiological adaptation to weightlessness, it might explain the continued increased excretion of electrolytes and the hyponatremia. Spacelab missions dedicated to the life sciences should allow the necessary renal experiments to be performed in space. On the first and second Spacelab Life Sciences missions, renal blood flow, glomerular filtration rate, central venous pressure, plasma volume, extracellular fluid, and a number of hormones and electrolytes in blood and urine will be measured as part of the same experiment. Food and water intake will be recorded during the mission, and all urine voids will be collected. Beginning at 3 h after launch, blood will be drawn at carefully controlled intervals. The first renal function test will start 3.5 h after launch, and central venous pressure will be measured from before launch to 12 h after launch. On the second and sixth days of flight, extracellular fluid and plasma volume will be measured. The results of this experiment should indicate how renal blood flow is affected by weightlessness and how it might affect other physiological variables.

3. ERYTHROPOIESIS

A decrease in red cell mass is one of the most consistent findings in astronauts immediately after flight, and at least 2 weeks are required for recovery. An experiment was done on Spacelab-1[22] to determine whether the reduction in red cell mass is caused by decreased production or increased destruction of red blood cells. Erythropoietin (Ep), a hormone that stimulates red blood cell production, was measured as part of this experiment, the first time this hormone has been measured in blood samples taken during space flight.

Preliminary results were obtained by use of the fetal mouse liver assay, but this method was not considered to be sensitive enough to measure suppressed physiological levels of the hormone. When a radioimmunoassay method[7] became available, it was used to determine Ep level in three preflight, two inflight, and four postflight frozen samples from each of four crewmembers who participated in the study. When statistical contrasts were performed on pairs of consecutive days, it was found that the first inflight measurement (the second day of flight) was significantly lower (Fig. 2) than the last preflight measurement (1 day before launch). Blood levels of Ep were still reduced a week after launch and immediately after landing. The crewmembers had an average 15% decrease in red cell mass immediately after landing. There was a significant positive correlation between erythropoietin and reticulocyte number in this experiment, indicating that production of red blood cells was associated with erythropoietin level.

Production of Ep is affected by renal plasma flow, which has not yet been measured during space flight but may be increased most of the time during weightlessness. Reduction of renal blood flow by renal artery constriction has been shown to increase Ep production[8,9], but the reverse experiment has not been published because of the difficulty of measuring low levels of Ep in plasma. The relationship of plasma erythropoietin and renal blood flow in microgravity will be investigated when both are measured on the same integrated Spacelab Life Sciences mission.

4. CALCIUM METABOLISM

Parathyroid hormone and 1,25-dihydroxyvitamin D_3 have been the main focus of recent NASA studies of mineral physiology in flight. Circulating levels of these hormones measured during space flight and ground simulation have varied with duration of flight. However, in all cases calcium has been lost from the body.

Preliminary results of an experiment performed on Spacelab-2[34] indicate that levels of two metabolites of vitamin D, 25-hydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3, did not change significantly during flight. The metabolite 1α,25-dihydroxyvitamin

D_3, which is produced by the kidney and increases intestinal calcium absorption and resorption of calcium from bone, increased substantially in the first 2 days of flight. This suggests that the 1α,25-dihydroxyvitamin D_3 may help initiate the calcium loss from bone. In Spacelab-2 crewmembers who participated in the experiment, plasma calcium was indeed elevated early inflight when 1α,25-dihydroxyvitamin D_3 increased, and it returned to preflight levels late in the flight and at landing. During the postflight recovery period, however, when 1α,25-dihydroxyvitamin D_3 was only slightly decreased, plasma calcium exhibited its greatest change, a 5% decrease, which was probably associated with changes in other plasma electrolytes measured after the flight.

Investigation of the role of key metabolic hormones such as insulin, thyroxine and catecholamines is necessary for thorough study of calcium metabolism. The changes measured in insulin during space flight have indicated that a net catabolic state may exist[21]. Thyroxine has not yet been measured in blood samples drawn inflight. Comparison of preflight and postflight plasma thryroxine shows that thyroxine increased 11.5% and that this increase was highly significant ($P < 0.00001$). Triiodothyroxine decreased slightly, and thyroid stimulating hormone increased significantly (21.5%, $P < 0.005$). These results agree with those of Leach, Johnson, and Driscoll[24] for Skylab. Increased thyroxine during flight would probably contribute to a catabolic state and promote muscle atrophy and bone resorption. Negative calcium balance, hypercalcemia, and bone diseases such as osteoporosis have been observed in hyperthyroid patients[39], and thyroid hormone stimulates bone resorption *in vitro*[30].

Although high plasma levels of cortisol have been associated with bone mineral loss in humans under certain conditions, recent evidence from experiments in which weightlessness is simulated indicate that increased blood levels of glucocorticoids are not the main cause of bone mineral loss during space flight. In a suspended rat model in which only the hindlimbs were unweighted, calcium was lost only from the unweighted limbs[11]; if glucocorticoid had been a major cause of calcium loss, the loss probably would have been ubiquitous. Adrenalectomy did not prevent the decrease in bone mass in this model[3]. In human studies using bedrest as a weightlessness simulation, there is usually no increase in plasma cortisol[27]. Plasma cortisol did not change in cosmonauts on the Salyut-6 mission, but a loss of bone density was measured[37].

Calcium excretion may be influenced by many factors that affect sodium excretion. When diuresis is induced by loading with water or sodium chloride, and during acetylcholine-induced vasodilation, clearances of both sodium and calcium increase[6]. Calcium and sodium are excreted similarly when renal hemodynamics are altered. It is possible to dissociate renal excretion of these two ions by such actions as infusing parathyroid hormone, which increases calcium but not sodium excretion, and administering mineralocorticoids, which decrease sodium but not calcium excretion. Urine samples were not available from Spacelab-2, but plasma sodium and calcium did not change in the same direction, and in Skylab crewmembers urinary sodium and calcium did not change proportionately[26].

5. CONCLUSION

Our studies to date demonstrate the complexity of the systems that control fluid and electrolyte metabolism, erythropoiesis, and calcium metabolism. These areas are some of the most important in space medicine because of weightlessness effects such as orthostatic intolerance and decreased bone density. Future experiments on Spacelab missions and the Space Station will test the current working hypotheses about causes and prevention of problems associated with return to the 1-***g*** environment.

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MATH MODELLING AS A COMPLEMENT TO THE SCIENTIFIC INQUIRY OF PHYSIOLOGICAL ADAPTATION TO SPACE FLIGHT: FLUID, ENDOCRINE AND CIRCULATORY REGULATION

J I Leonard
MATSCO/
General Electric Co.
Washington DC, USA

R J White
NASA
Washington DC
USA

J A Rummel
MAP, Inc.
Houston, Texas
USA

ABSTRACT

This paper discusses the contribution that mathematical modeling and computer simulation have made to the understanding of some of the problems arising during weightless space flight. A number of examples are provided from the areas of fluid, endocrine and circulatory regulation to illustrate the utility of modeling as an adjunct to the process of scientific inquiry, especially in the development and theoretical testing of hypotheses. The models were used to examine both the acute and chronic phases of space flight. Many paradoxical results appear when data obtained during chronic adaptation is interpreted using theories which pertain to acute adjustments. The modeling process has provided a means of developing a theoretical basis for interpreting the chronic adaptive phase of flight.

Keywords: mathematical models, computer simulation, physiological adaptation to microgravity, fluid regulation.

1. INTRODUCTION

Mathematical modeling is generally useful for studying systems that are poorly understood, complex and data poor. It is also valuable in situations in which experimentation is costly or impossible. This would certainly seem to apply for the field of space physiology which is still in its infancy. For these reasons, mathematical modeling and computer simulation have been in use by NASA for a number of years as one approach for understanding physiological adaptation to microgravity (Ref. 1). Modeling has been used principally as a means of organizing and interpreting the data within a given discipline. But also it has proved useful in integrating data across disciplinary lines because adaptation to microgravity certainly is the result of changes from a large number of physiological systems acting in concert. We believe modeling has contributed to understanding these changes and this paper will describe a portion of this effort.

Although a number of examples and approaches will be discussed, the underlying theme is that modeling is a true complement to the traditional process of scientific inquiry, in a manner similar to the use of experimental models. Models, experimental or mathematical, are certainly capable of suggesting explanations and making predictions regarding the system under study. However, those explanations and predictions are often not as important as the questions we are forced to ask in order to understand why a model behaves as it does or why it doesn't behave as we think it should. Thus models should be judged, not solely on the basis of their ability to predict future events but on the power they offer in raising the critical questions. These critical questions then become the basis for other key aspects of the scientific process-hypotheses development and the experiments to test them.

The task of developing a sound understanding of the space-flight adaptation processes is confounded by the lack of adequate data in some cases and by an incomplete physiological epistemology in other cases. Modeling however, provides a powerful framework in which to place what is known about a particular situation (data), or about a physiological system (relationships), along with what is suspected about that system (hypotheses) and permits us to assess their consistency under many situations.

The examples of modeling which are presented here are all concerned with fluid-electrolyte metabolism and the renal-endocrine control of that system as it adapts to a new environment. Two particular mathematical models have been especially useful in this effort and these will be summarized briefly in the next section.

2. MODELS AND TECHNIQUES

A model which has proved invaluable in these studies was developed some time ago by Arthur Guyton for the study of overall circulatory, fluid, and electrolyte regulation (Ref. 2). This model contains subsystems which describe fluid and electrolyte exchanges between the major volume compartments, cardiovascular and renal dynamics, hormonal control, and blood volume regulation including separate control of plasma and red cell components. Both short-term and long-term adaptive control mechanism are represented. Recent modifications include adding leg vascular and tissue compartments, gravity dependent circulatory elements, and a natriuretic factor. These additions provide the capability for simulating postural

changes and fluid shifts between upper and lower body. The entire biological control system represented in this model is extremely complex but it offers to the physiologist an opportunity to examine complex interactions, simultaneous stimuli, and steady state as well as dynamic behavior.

A second and less complex model was developed by Leonard et al (Ref. 3) to examine the more limited area of erythropoiesis control. The model incorporates the current understanding of the dynamics of red cell production and associated feedback regulation based on the balance between tissue oxygen supply and demand. Simulation studies with this model have provided useful insights into the still perplexing problem of the "anemia" of space flight. It is possible to use this model on a stand-alone basis, and it has also been incorporated into the modified Guyton model. The Guyton and Leonard models together form the theoretical basis to study total blood volume regulation in space flight (Ref. 4).

The simulation of headward fluid shifts in the modified Guyton model is most easily simulated by altering the angle of tilt. This changes the direction and magnitude of the gravity vector as it affects blood pooling in the legs. Once the angle of tilt is specified and the model simulation begins, fluids become redistributed by the elastic forces of the tissues and vessels in a manner favoring upper body hypervolemia. Subsequently, feedback controllers respond by regulating blood flow, blood pressure, and blood volume toward more normal values.

Simulations of space-flight using the stand-alone model of erythropoiesis were accomplished by simply removing about 10 percent of the plasma volume. (The plasma volume in this model is fixed and controlled by the user, while it is adjusted homeostatically in the Guyton model). The resulting hemoconcentration provides an appropriate hyperoxic disturbance that results in a realistic simulation of the flight data.

The practical approach for using these models is illustrated in Figure 1. Data from space flight or ground-based analog studies are used for two purposes. First, to generate hypothesis and second, to verify the models by comparing the theoretical and actual responses. If required, the model's responses could be altered, by formulating one or more hypotheses, and modifying the model in accord with this formulation. Computer simulation techniques could then be applied to test these hypotheses and assess their plausibility. These techniques might include merely changing the value of a fixed parameter (ie., adjusting the gain or set point of a control loop), clamping the value of a variable (i.e. opening a feedback loop), or in some cases, introducing an entirely new control mechanism into the model. The most plausible of these results may then become a starting point for the design of validation experiments in the laboratory and eventually lead to permanent improvements of the model. This interaction between model simulation and experiment studies is valuable and synergistic. The approach discussed above is known as hypothesis development and testing and is used principally to help interpret experimental data. Some of the benefits which have been derived from hypothesis development include the ability to explain paradoxical behavior, to assess alternate hypotheses, to predict difficult to measure quanti-

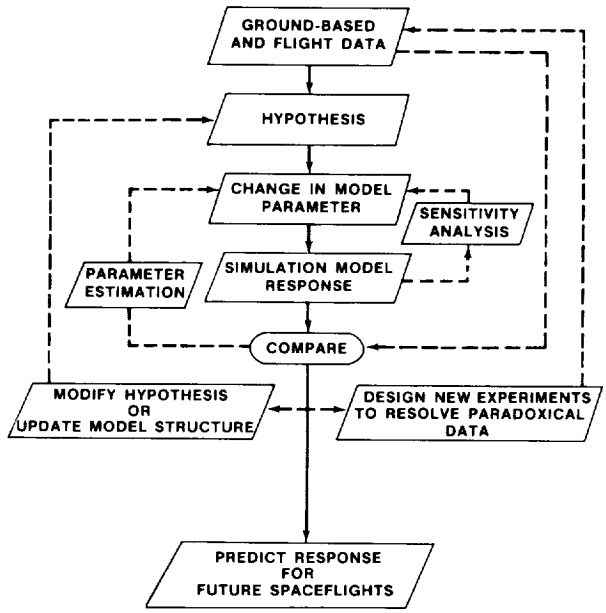


Figure 1. Use of simulation models in space flight program

ties, to isolate mechanisms and physiological pathways, and to synthesize scenarios consisting of multiple hypotheses.

Another approach to modeling, is often employed to study the feedback control behavior of the underlying physiological system. While the former approach requires rigorous model-to-data comparison, the study of system behavior often is characterized by model-to-model comparison and therefore does not require new data in addition to that used to formulate the model. In Figure 1, this system behavior approach to modeling is represented by the "sensitivity analysis" technique. Sensitivity analysis is used to reveal those parameters which have the most sensitive influence on a system. Other similar techniques that have been used include parametric analysis, dynamic vs steady-state analysis (to look for non-linear effects), and feedback stability analysis. Finally, a third approach is the "parameter estimation" technique in Figure 1 and is a means of determining the value of a model parameter which produces an optimum "fit" between model and experimental responses. Of all the techniques mentioned, this method of curve-fitting is most commonly employed by physiological simulation analysts. It has not been widely used in the space-flight studies, however, and is included here only for completeness.

The remainder of the paper will discuss the results of modeling analyses in addressing specific problems in the areas of acute fluid loss, blood volume regulation, control of central venous pressure, and hormone behavior.

3. ACUTE FLUID SHIFTS

Perhaps the most dramatically visible event that occurs to the physiological systems immediately upon entering microgravity is the shift of fluids, which are usually pooled in the legs by gravitational forces, to the upper body. Associated with the measured reduction in leg volume is the observation of distended cephalic veins and tissues. This shift of fluids is thought to lead to a sus-

tained loss of body fluids, especially plasma volume.

A theory to explain the reduction in plasma volume had developed during the early years of manned flight, namely that the shift of fluid into the upper body would be interpreted as an increase in effective blood volume. According to the conventional wisdom at the time, homeostatic mechanisms, centering around the Gauer-Henry (ADH) pathway, would appropriately correct this blood overload by a diuresis (Ref. 5).

In spite of the attractiveness of this theory, a number of problems remained unresolved. It appeared rather simplistic to ascribe the loss of plasma volume in space flight to only one pathway inasmuch as there exist a large number and types of blood pressure regulating mechanisms (see Figures 2 and 3). Also, attempts to provide verification of this hypothesis were not always successful; neither the diuresis nor the reduction in ADH have yet been observed in space. Finally, and most important, there were conflicting data emanating from ground-based hypogravic stress studies. Although water immersion studies supported the theory stated above, a number of bedrest studies indicated otherwise. Decrements in leg volume were smaller for bed rest than space flight, and a number of other changes were often opposite to that predicted by theory, including those for blood pressure, hormones, and renal excretion.

It was at this time that a systems analysis, including mathematical modeling of fluid regulation in space flight, was initiated with a view of bringing a more systematic and theoretical approach to bear on the issues described above. The first step was to describe current knowledge and theories in qualitative terms (Ref. 6). As indicated in Figure 2, central hypervolemia resulting from weightlessness activates sensitive volume receptors and other mechanisms, which in turn act to eliminate the excess fluid by several available pathways. Three major pathways exist by which the overload of plasma volume can be corrected: reduced fluid intake, diuresis, and transcapillary fluid

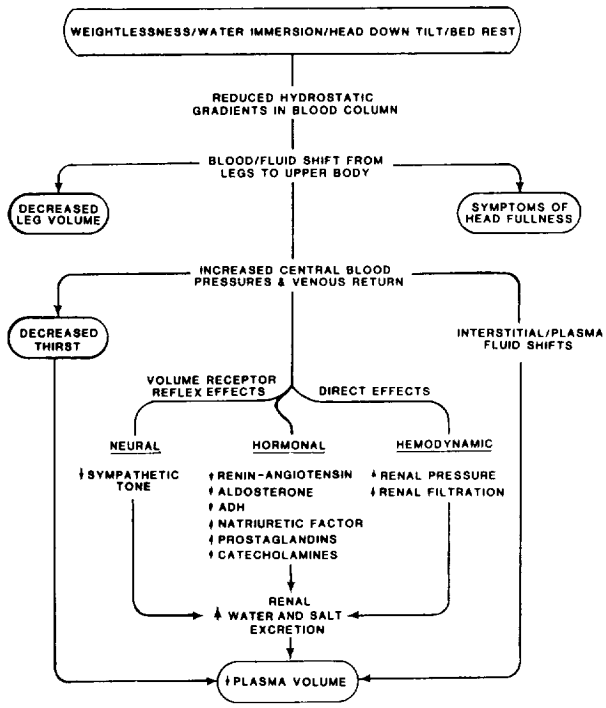


Figure 2. Fluid-shift hypothesis

transfer. Of these, the portion of the hypothesis related to renal regulation is the most complex, and can be further separated into neural, hormonal, and hemodynamic factors. The pathways relating these three types of renal mechanisms, which ultimately could result in a diuresis, were the subject of a more extensive analysis which is summarized in Figure 3 and described fully elsewhere (Refs. 7, 8). It is quite clear that a number of interrelated and parallel pathways exist for reducing the plasma volume, especially in the renal system. Moreover, computer simulation of these events provided additional insight and clarification regarding which pathways may predominate under various conditions encountered in space flight.

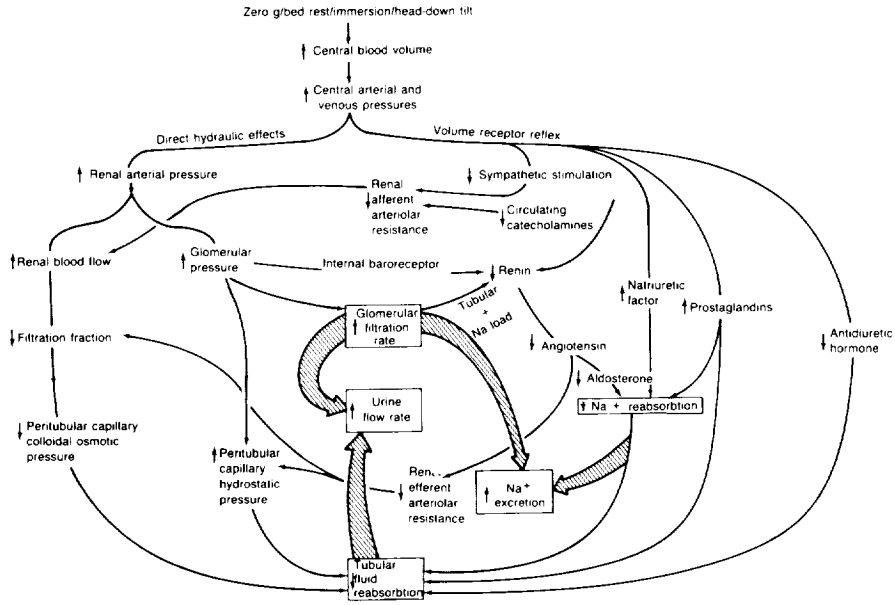


Figure 3. Acute renal-endocrine disturbances in hypogravity

Theoretically, it is possible for a reduction in plasma volume to occur by any one of the three major routes shown in Figure 2. In practice, it appears that each pathway's contribution depends on its unique characteristics and the circumstances of the experimental study. For example, on Skylab most of the fluid losses can be accounted for, mathematically at least by deficit drinking (Refs. 6, 9) while during water immersion and head-down tilt studies, fluid losses are related to a renal diuresis. In view of the ground-based results, the lack of a measured diuresis during the first inflight day has been particularly puzzling. However, computer modeling studies have suggested that when fluid intake is restricted (as exhibited during the first few days by most space crews), an acute diuresis can be obscured in a 24-hour pooled urine collection because of a subsequent anuresis. These theoretical studies also predicted that while restricted drinking contributes to a reduction in body fluids, it does not abolish the diuresis effect completely; accurate measurement of the diuresis may require careful and continuous monitoring. Conversely, it is predicted that there will be an easily measurable diuresis during the first 4-6 hours in normally hydrated subjects. The simulation analysis has also revealed that the transcapillary filtration mechanism indicated in Figure 2 is self-limiting as a means of relieving central hypervolemia and may only be important during the first few hours of weightlessness. Thereafter, lymph flow or inward filtration may restore interstitial volume to normal. This self-limiting phenomenon occurs because plasma colloidal concentration increases as fluid moves into the interstitium, which opposes further filtration. The limited data on this subject indeed suggests that interstitial fluid volume remains relatively constant even after a month or more of space flight (Refs. 6, 10). Taken as a whole, these analyses indicate that in the well-hydrated subject, the kidneys can be expected to be the principal avenue of fluid regulation during weightlessness.

Even more important than the above, was that simulation of the mathematical model resulted in clarification of the dynamic nature of the fluid system as it responds to the acute onset of weightlessness. Furthermore, the dynamic behavior, by itself, appears to explain some of the paradoxical experimental results that were being reported. This is illustrated most clearly in a computer simulation of the first 24 hours of hypogravity (Refs. 1, 11, 12) shown in Figure 4. The validity of these model responses is apparent from the close agreement to the head-down tilt studies conducted by Blomqvist and co-workers (Ref. 13). During the first several hours the mathematical model predicts a number of changes in fluid volumes, hemodynamics, and renal-endocrine function (i.e., see open circles in Figure 4), all of which are in essential agreement with the hypothesis diagram of Figure 1. If measurements were taken at any time later than that (i.e., see filled circles in Figure 4), the model predicts that one may find hormone levels elevated (angiotensin, aldosterone, ADH), renal excretion stabilized or reduced, or venous pressures below normal. Indeed, such "paradoxical" findings have in fact been observed in space flight (Refs. 9, 14, 15). However, the simulation analysis suggests that these results are merely the normal response of a highly complex feedback system which has succeeded in correcting the central hypervolemia at the expense of a stabilized reduction in plasma and leg volume. In fact, except for fluid volume changes, all other relevant variables examined exhibit a transient biphasic behavior, displaying, in some cases, an overshoot phenomena. These model results strongly suggest that if confirmation of the fluid redistribution hypothesis is to be obtained, then the measurements should be conducted in well hydrated individuals within a few hours after launch. By the time the fluid volume decrements can be measured, it may be too late to capture the events which caused these losses.

In summary, a modeling analysis of the fluid-shift hypothesis has revealed that the hypothesis is based on concepts of acute fluid regulation, specifically, those which are related only to volume and pressure disturbances. In the real system, there are both short-term and long-term control mechanisms. Therefore, the fluid-shift hypothesis pertains only to a static slice of time, during the first few hours of weightlessness, while the real system is actually in dynamic motion.

For the most part, a reasonable understanding currently exists regarding the possible mechanisms of acute fluid disturbances in space flight (although most of the data is derived from ground-based experimental models). What is needed is an equally broad theory of long-term fluid, electrolyte and hormonal regulation to help explain the large data base accumulated from bed rest and space flight studies of weeks and months in duration. The following sections describe several different problem areas of long-term control during space flight, and suggest possible mechanisms derived from a systematic simulation study utilizing the mathematical models. These aspects are concerned with long-term control of blood volume, venous pressure, and hormone secretion.

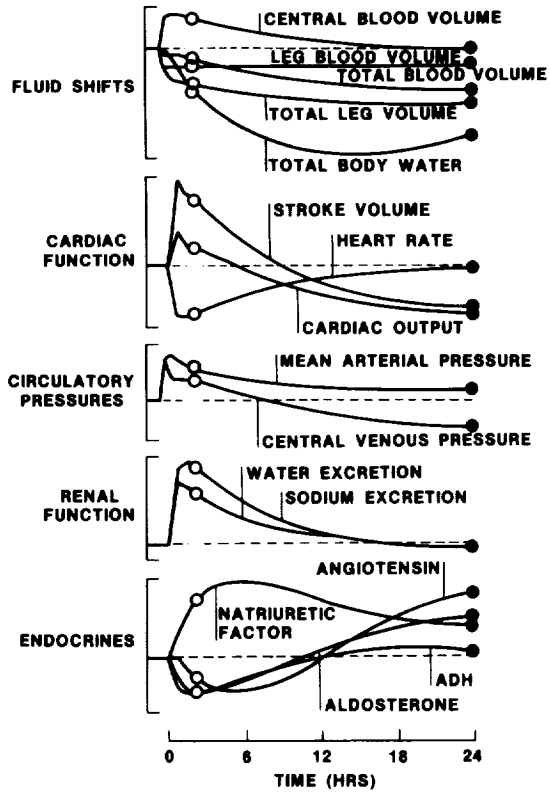


Figure 4. Simulation of head-down tilt (-6 degree)

4. BLOOD VOLUME REGULATION

A typical finding in astronauts returning from space flight is a reduction in total circulating blood volume of about ten percent (Ref. 16). Although not measured directly during flight, this blood volume reduction is believed to be the result of an acute plasma volume loss, followed by a more gradual loss of red cell mass, a finding commonly reported during bed rest (Ref. 17). Figure 5 illustrates the data for blood volume changes reported for the three Skylab missions (Ref 10). Several important questions related to plasma and blood volume regulation were subjected to analysis using model simulation. In particular, what determines the extent of plasma volume loss? What factors are involved in the loss of red cell mass? And, how is long-term regulation of total blood volume accomplished in space flight?

As discussed in the previous section, the etiology of the plasma loss is most likely a direct response to headward fluid shifts (i.e. central hypervolemia). Two different types of fluids, blood and interstitial filtrate, are shifted cephalad during space flight. Using computer simulation techniques it is possible to distinguish between the separate effects of blood shifting from the legs versus tissue filtrate shifting from the legs during the onset of weightlessness. Figure 6 summarizes the results of two model simulations in which 500 ml of either blood or filtrate from the legs were forced from the leg blood vessels or from the leg tissue compartment, respectively. Once this somewhat artificial initiating maneuver was completed (in a matter of minutes), the fluids distributed themselves in a manner consistent with hemodynamic factors.

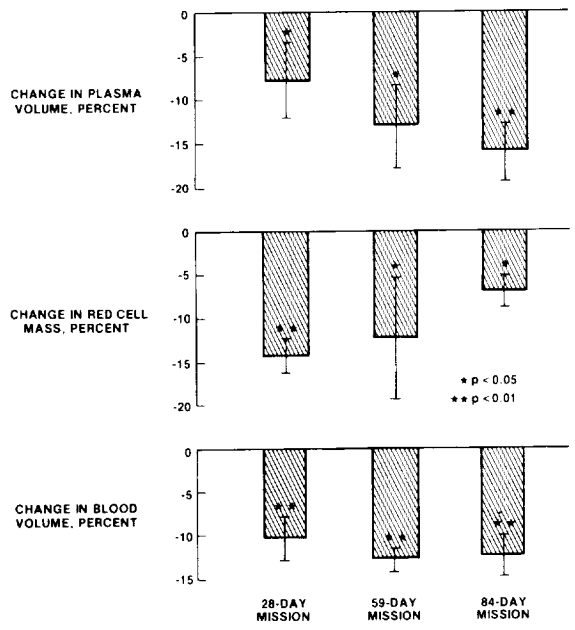


Figure 5. Blood volume alterations in Skylab crew

The top panel of Figure 6 indicates the rate at which equal amounts of these two types of fluids were shifted from the legs. Although most of the responses shown in Figure 6 differ for the two fluids, the disparity in the response of the blood volume compartment is perhaps the most dramatic. For the case of blood shifting from the legs, the

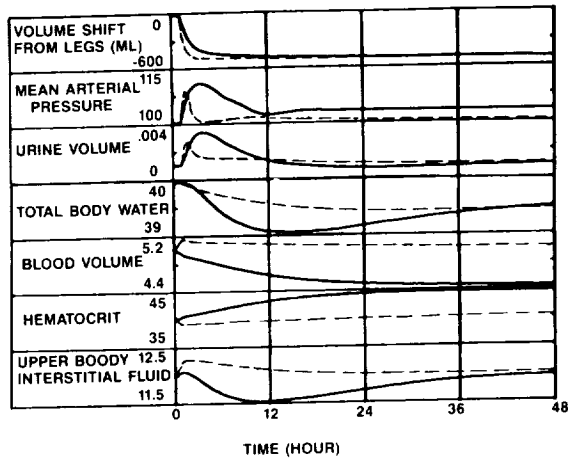


Figure 6. Blood vs. filtrate shift from legs
500 ml blood shift from legs (———)
500 ml filtrate shift from legs (- - - -)

blood volume decreases over time (as we have come to expect for hypogravic maneuvers). Conversely, when leg filtrate shifts in the circulation, the blood volume first increases and then returns to control levels, but never falls below control. (The hematocrit responses merely mirror the blood volume responses because red cell mass is reasonably constant). This seems to indicate that the blood volume decrease in hypogravity is ultimately a result of blood shifting from the legs and activating the renal pathways (Figure 3), which in turn relieves the upper body volume disturbance. Leg filtrate, on the other hand merely enters the vasculature in the legs and exits the vasculature in the upper body (either to the kidneys or temporarily into the tissue compartment). Notice that the model predicts that in the case of blood shifts, the blood volume is depleted by about 500 ml, an amount similar to that which was originally shifted from the legs.

It may be possible to speculate from these studies that the blood volume loss in space flight is a result of, and similar in magnitude to, the shift of blood from the peripheral circulation in the legs toward the upper body. In terms of control theory, the set-point for blood volume regulation has been changed or reset. Removal of interstitial fluid from the legs contributes to overall body dehydration but not to blood volume loss per se. Furthermore, as predicted in Figure 4, the depletion of blood volume (and possibly stress relaxation of the large veins) might restore the expanded central volume and elevated pressures to their preflight levels. In other words, fluid congestion of the upper thoracic cavity (not necessarily including the head and neck tissues in which some excess fluid presumably remains) is predicted to be a short-lived phenomena in space flight. This prediction is supported by recent findings of reduced venous pressures in astronauts (Ref. 14).

The failure of plasma volume to return to normal during prolonged flight (even with a normal and **ad libitum** fluid intake), as noted in Figure 5 is presumptive evidence of the active involvement of blood volume controllers and perhaps an effective change in volume set-point. Thus, although an expected diuresis has not yet been observed early in a flight, volume receptors and renal excretion pathways may be continually responding to the tendency for fluids to pool headward, thereby acting

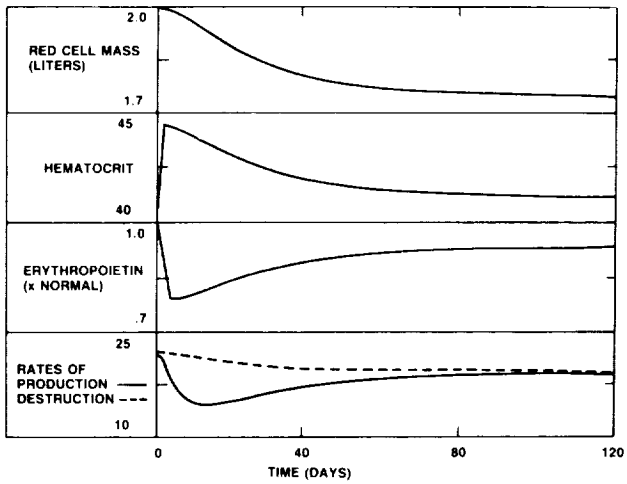


Figure 7. Response to a step decrease (300 ml) of plasma volume

to maintain a reduced blood volume. This hypothesis could be tested by administration of a fluid load in space flight. The model predicts that any fluid load would eventually be excreted and the plasma volume would ultimately be maintained at the reduced levels consistent with the effective change in total blood volume set-point.

The blood volume changes noted above primarily reflect the plasma component of blood. An important question concerning blood volume regulation in weightlessness is the fate of red cells. As is well known, the red cell mass almost invariably declines in bed rest and space flight. The cause has not yet been established (Ref. 16). An extensive modeling effort of the erythropoiesis system has provided additional insight into the nature of the observed red cell mass changes (Refs. 4, 17, 18). Several possible mechanisms for the "anemia" of space flight were suggested by simulation analysis of the model of erythropoiesis regulation. These include changes in renal blood flow, alterations of oxy-hemoglobin affinity, reduction of plasma volume, moderate hemorrhage or hemolysis, and inadequate caloric intake. No single mechanism appears to be solely responsible. One of the more attractive implications of the model analyses is that the hemocentration resulting from plasma loss, a frequent finding in bed rest and space flight (Refs. 16-19), is possibly a major factor leading

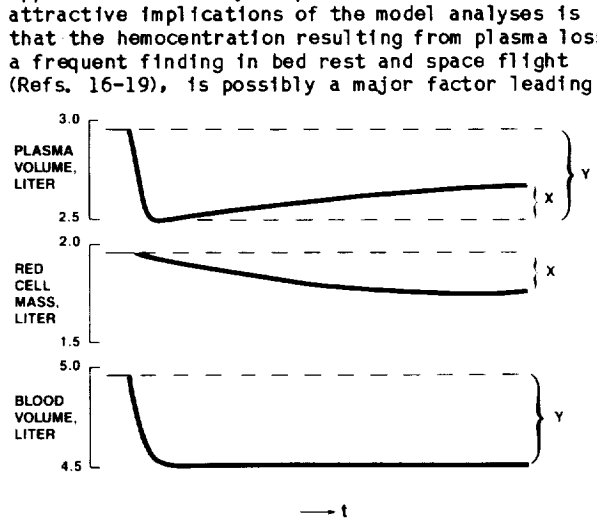


Figure 8.

Relationship between blood volume components during space flight simulation

to the loss of red cell mass. Accordingly, the increase in blood hemoglobin concentration would be expected to enhance oxygen delivery to the tissues, particularly the renal oxygen sensors which are involved in activating the secretion of erythropoietin. An effective overload of oxygen to these renal sites would be expected to suppress erythropoietin levels, which in turn could dramatically decrease red cell production. Without new red cells entering the circulation, the normal attrition of erythrocytes would begin to deplete the red cell mass. This process could continue until rates of red cell production and destruction equilibrate (see Figure 7). This scenario is based on the plausible concept that red cell production in space, as on earth, is regulated by a balance of oxygen supply and demand.

An equally intriguing and unexpected observation from the modeling study is summarized in Figure 8. A simulation of hypogravity was achieved by the same head-down tilt maneuver that was employed for the study shown in Figure 4. The rapid fall in plasma volume was caused by the mechanisms described in Figures 2 and 3. The more gradual depletion of red cells resulted from the hemoconcentration mechanism described above. The model predicts that blood volume will be maintained constant at a new and reduced level, consistent with the concept of a change in set-point. As a result, the plasma volume (which is free to change in the Guyton model) begins to slowly recover from its minimum value at a rate which exactly replaces the volume equivalent of red cells which are lost. Although highly speculative, this hypothesis is supported by the data shown in Figure 5. In spite of the variability of plasma volume and red cell mass among the three missions, the blood volume remains relatively constant. Taken as a whole, this suggests that total blood volume, rather than plasma volume or red cell mass, is tightly regulated. Analysis of other flight data may reveal whether this is a general effect.

5. CENTRAL VENOUS PRESSURE

Closely related to the phenomena of acute fluid shifts is the response of the central venous pressure during hypogravity. A study of disturbances of venous pressure provides another example of how modeling can be used in the scientific process. Central venous pressure assumes importance in the physiological monitoring of fluid redistribution in microgravity because it reflects the status of central blood volume. For example, the time course of the cephalad fluid shift and its subsequent normalization is likely to be revealed by monitoring central venous pressure. However, this fundamental information is still lacking because of the inherent difficulty in directly measuring central venous pressure. Nevertheless, central venous pressure has been measured or inferred in a variety of related situations and this data is summarized below.

The first measurements of the expected increases in central venous pressure as a result of hypogravity were obtained during water immersion studies. Arborelius, et al (Ref. 20) measured a dramatic increase in right atrial pressure (about 15 cm H20) ten minutes following immersion. Echt (Ref. 21) duplicated these results and determined that central venous pressure remains elevated for at least three hours. As a result of these studies, some believed that central venous pressure would remain quite high for an indeterminate period of time in

space flight. In fact, there was some concern regarding the possibility of right heart congestion (Ref. 22). It was not until Blomqvist and co-workers (Ref. 13) reported on their head-down tilt studies that it was demonstrated that central venous pressure can behave in a highly dynamic manner, first increasing and then decreasing below control levels. Although the increase in central venous pressure was expected, the magnitude of the increase in head-down tilt was much less than observed in the earlier water immersion studies. In addition, the subsequent decrease below control of central venous pressure was unexpected by most investigators. Only recently, have the first inflight measurements been obtained. Bungo (Ref. 23) measuring echocardiographic left diastolic volume and Kirsch, et al (Ref. 14) measuring peripheral venous pressure have both inferred decreased venous pressure after six hours and 22 hours following launch, respectively.

The data presented above does not appear wholly consistent among the various studies nor with the prevailing notions of fluid shift hypothesis (Figure 2). The water immersion results showing increased venous pressure are in obvious accordance with the hypothesis that headward shifts of fluid from the legs will expand the central blood volume. In that light, however, the space flight results indicating decreased venous pressure are confusing - especially because of concomitant observations of fluid congestion in the head and neck. Only the head-down tilt studies of Blomqvist and co-workers (Ref. 13) successfully reconciled these sets of measurements. However, no satisfactory explanations for the observed decrease in venous pressure have yet emerged, either for head-down tilt or space flight.

The mathematical modeling of the circulatory responses to hypogravity, including central venous pressure, was first conducted soon after the water immersion studies had been reported (Ref. 24). In the first attempt to simulate supine bed rest, the Guyton model indicated results very similar to those reported by Blomqvist some years later. However, because the prevailing opinion of that day was that central venous pressure would remain elevated in space flight, the modeling prediction that the venous pressure would quickly decline to below normal (see Figure 4) was not given serious consideration. Following the Blomqvist report, however, the modeling of central venous pressure was revisited (Ref. 12) and a description of this more recent modeling study is summarized below.

A closer examination of the Guyton model indicated that only three factors could be responsible for the decline in venous pressure toward normal after an initial rise due to cephalad fluid shifts. These factors are: an increase in venous compliance or stress relaxation, a decline in blood volume, and an increase in total peripheral resistance. All of these adjustments occur in the model following the initiation of a headward fluid shift; they are parts of an automatic feedback response which attempts to normalize an increase in blood pressure. Because of their role in blood pressure regulation, all three factors could be expected to return central venous pressure to normal. However, it was not obvious at first which one or more of these factors were responsible for the decline of central venous pressure to **below** normal levels. By using special simulation techniques it was possible to isolate the total peripheral resistance as the most important factor involved in this process.

Additional analyses were performed with the model to isolate the mechanisms which permit total peripheral resistance to increase. In Figure 9, the dynamic behavior of four factors which control total peripheral resistance in the model is shown during a head-down tilt simulation. The response is quite complex, demonstrating the utility of a model in sorting out and integrating this type of behavior. For the first few hours autoregulation causes total peripheral resistance to increase in an attempt to locally shut down an overperfused tissue; viscosity gradually increases because of hemoconcentration; angiotensin responds to a high pressure stimulus by falling in value; and the autonomic behavior reflects baroreceptor input. After 24 hours only the angiotensin and the viscosity effects remain as stimuli to explain the sustained increase in total peripheral resistance. These model changes can obviously be translated into an hypothesis for experimental testing.

The ability of viscosity (hemoconcentration) to control total peripheral resistance was carefully examined as the simulations shown in Figure 10 indicate. In this figure, simple infusions of similar volume are performed with either plasma or whole blood. The responses of blood volume and arterial pressure are nearly identical in each case, although the hematocrit response is quite different. Also, the hematocrit and total peripheral resistance responses are parallel for each infusion, reasonably suggesting that the former variable is controlling the latter. Furthermore, the response of whole blood infusion appears very similar to the response for head-down tilt (Figure 4) except for the blood volume which, of course, is elevated for the case of infusion and depressed for the head-down tilt case. This similarity is predictable if one thinks of head-down tilt as an autoinfusion of blood from the legs to upper body. In that case, the blood volume response to whole-blood infusion (Figure 10) is analogous to the central blood volume response of head-down tilt (Figure 4). Even more important and germane to this discussion is the fact that venous pressure declines much further below control in the simulation of whole blood infusion compared to the plasma infusion. This demonstrates that a decreased venous pressure is possible without postural change, merely by creating a hemoconcentrated

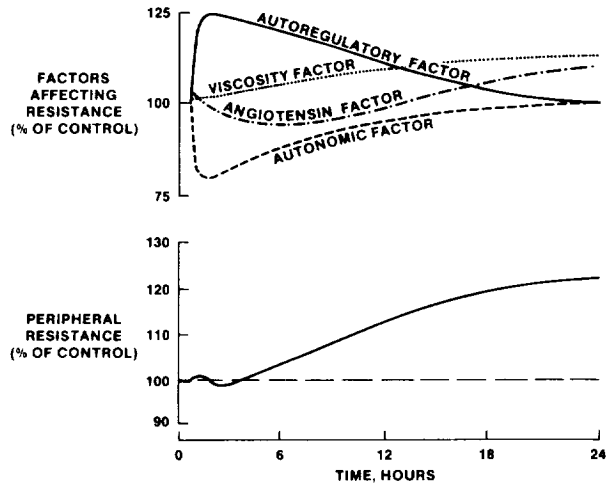


Figure 9. Factors controlling peripheral resistance during head-down tilt

condition. Put more simply, any mechanism which causes total peripheral resistance to increase will tend to lower venous pressure. Although this relationship is known, it is proposed here as the operative mechanism underlying the venous pressure changes observed in space flight.

As a partial validation of this hypothesis, it was possible to compute total peripheral resistance during head-down tilt using Blomqvist's data for arterial and venous pressure and cardiac output. Values for resistance are in agreement with the model with regard to direction, magnitude and temporal relationships. Also, the recent echocardiographic data of Bungo (Ref. 23) indicates an increase in peripheral resistance during space flight. Other experimental studies will be needed, however, to conclusively link changes in resistance with venous pressure and to determine if other factors such as venous compliance can contribute significantly to the decline of venous pressure. The currently proposed experiments for Spacelab on humans and rats will test these relationships (Ref. 25). For periods of time longer than can be studied in the normal one-week Shuttle flight, the model predicts that the elevated peripheral resistance will decline toward baseline levels thereby permitting venous pressure to return towards its baseline as well. Testing this hypothesis will require the long exposure times to weightlessness expected for space station inhabitants.

6. HORMONE REGULATION

A group of renal-regulating hormones consisting of anti-diuretic hormone, aldosterone, and angiotensin, has been the focus of many space flight related studies (Refs. 13, 26, 27). These hormones regulate the ionic concentration of body fluids, particularly, the concentrations of sodium and potassium. A knowledge of inflight hormone disturbances should therefore, provide insight into the status of the fluid-electrolyte and renal systems. However, the findings from space flight have been difficult to interpret or to reconcile with endocrine data obtained from one-g analogs of weightlessness.

Previously, we have organized the endocrine data from a number of hypogravic studies, whether performed in one-g or zero-g, into a qualitative, composite description (Refs. 6, 28). That analysis was based on the assumption that various maneuvers such as water immersion, head-down tilt, bed rest and space flight are parts of a time continuum. All these stresses have the common characteristics of an acute reduction in hydrostatic gradients and a resultant headward shift of fluid. Over longer periods of time, these maneuvers lead to reductions in body water, plasma volume, and electrolytes. In this construct, a six hour water immersion study should indicate the early responses to hypogravity, while a one-week bed rest study should provide the later responses, and a 24-hour head-down tilt study would provide intermediate information. Although these assumptions are not strictly valid, they will provide a point of departure for collating a diverse set of data. The results from such an analysis indicate that the acute hypogravic responses (during a period for which comparable space flight data are lacking) for the three hormones of interest lead to suppressed plasma levels, and that this can be explained on the basis of pressure-volume disturbances. However, the longer-term responses and their control mechanisms are much less clear. In the following analysis, a reconciliation of the differences between the acute and chronic responses to hypogravic stresses is attempted.

A schematic description of the factors which influence the three hormones (as they are represented in the mathematical model), reveal that each hormone is responsive to two general types of controlling stimuli: volume disturbances and electrolyte disturbances (Figure 11). For convenience, the stimuli are shown in Figure 11 in the direction that causes each of the hormones to increase in value. The volume stimuli (as reflected by atrial, renal, or arterial pressures) may provide control only during acute disturbances, because of the existence of several types of adaptive mechanisms indicated in Figure 11, and because the volume disturbances are often corrected by efficient volume-regulating mechanisms (Ref. 29). However, the influence of the electrolyte disturbances (as reflected by plasma sodium and potassium concentrations) is not known to adapt over time. Therefore these electrolyte sensing systems provide a more powerful type of long term control than volume sensors.

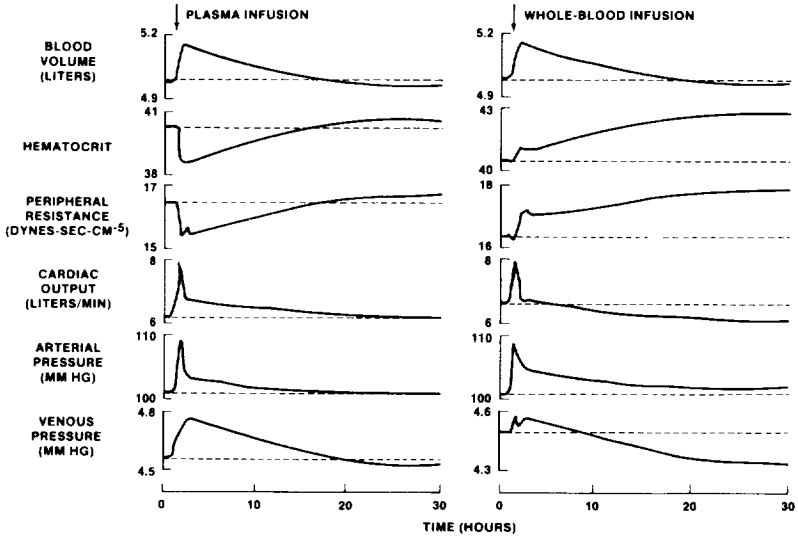
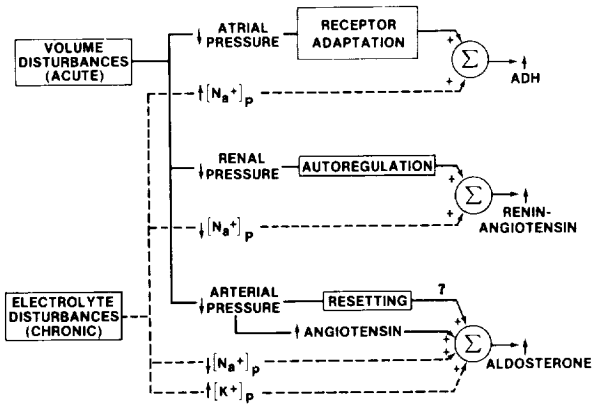


Figure 10. Simulated effect of plasma or whole blood infusion on hemodynamic responses



INFLUENCE OF VOLUME (——) AND ELECTROLYTE (- - - -) CONTROLLERS ON HORMONAL SECRETION

Figure 11.

All of the hormone stimulating factors shown in Figure 11 are known to change at one time or another during hypogravic maneuvers. For example, during the onset of weightlessness, blood pressures are likely to become elevated. Also, plasma sodium is frequently reported to be depressed sufficiently to suppress ADH secretion and elevate angiotensin. Plasma potassium levels (which have a much more powerful effect on aldosterone than plasma sodium levels) may vary upward or downward depending in part on muscle atrophy, metabolic intake, and excretion. These various changes, occurring simultaneously, complicate any attempt to perform an integrated analysis of hormone behavior.

An example of how computer modeling may be useful to account for the dynamics of endocrine control during space flight is presented here for the case of ADH changes (Figure 12). According to the algorithms embedded in the Guyton model, ADH is assumed to be under dual control of atrial (venous) pressure and plasma sodium concentration. The following assumptions are made regarding these stimuli under weightless conditions as shown in Figure 12: a) the central venous pressure response is similar to that found during head-down tilt; b) hyponatremia develops within several days; and c) ADH is primarily pressure/volume sensitive during the acute phase which may last until pressures begin to decline toward control levels, after which time the sensitivity gradually shifts to favor osmo-control due to some form of volume-receptor adaptation or pressure normalization. That ADH is primarily responsive to chronic osmotic changes in space flight is also consistent with the view that this hormone is a powerful long-term controller of plasma osmolarity (Ref. 29).

Although based on several untested assumptions, this hypothesis appears to explain the average ADH response as measured in the Skylab crew during the first month in space (see Figure 13). The complex triphasic response of ADH predicted by the model appears to be reflected by the space-flight data. Specifically, an early decrease in ADH during the first flight day (when ADH was not measured) can be inferred from water immersion studies, head-down tilt studies, and the first postflight day. Similarly, ADH is diminished during the second half of the first month in space. Between these two points in time, ADH may be in transition due to competition between venous pressure and osmo-control. Computer analyses of aldosterone and angiotensin indicate similar complex waveform responses for all three renal-regulating hormones (Refs. 28, 30). In the light of this hypothesis it is proposed that the long-term behavior of ADH, aldosterone, and angiotensin in space flight can be explained as chronic adaptation to metabolic factors.

An additional model prediction that remains to be confirmed is the existence of a natriuretic hormone (Figure 4) which responds to blood pressure disturbances and which can produce elevated levels of urinary sodium and hyponatremia in spite of elevated aldosterone levels. The natriuretic factor was added to the Guyton model for the primary purpose of simulating long-term hyponatremia. No other plausible change to the model was successful in producing this condition without creating adverse responses in other related systems. Without the presence of the natriuretic factor, the etiology of hyponatremia in space flight remains unresolved and puzzling because aldosterone was elevated and ADH suppressed, conditions that should promote correction of hyponatremia. Although the adaptive value of a hyponatremic extracellular fluid is not clear, hyponatremia is known to activate the renin-angiotensin system, induce hypersecretion of aldosterone, depress thirst, depress ADH secretion and promote renal excretion of water, all of which were noted to varying degrees in the Skylab crew. One unanticipated effect of hyponatremia that was revealed, at least in the model system, was a preservation of almost a liter of intracellular fluid. Fluid leaves the cellular compartment as potassium is depleted, and this action is opposed by a reverse osmotic gradient as plasma sodium levels decline, even by a few percent.

The long-term response of renal water excretion during hypogravity is shown for a month-long space flight in Figure 13. In Skylab, evaporative water loss was shown to be diminished by approximately 10

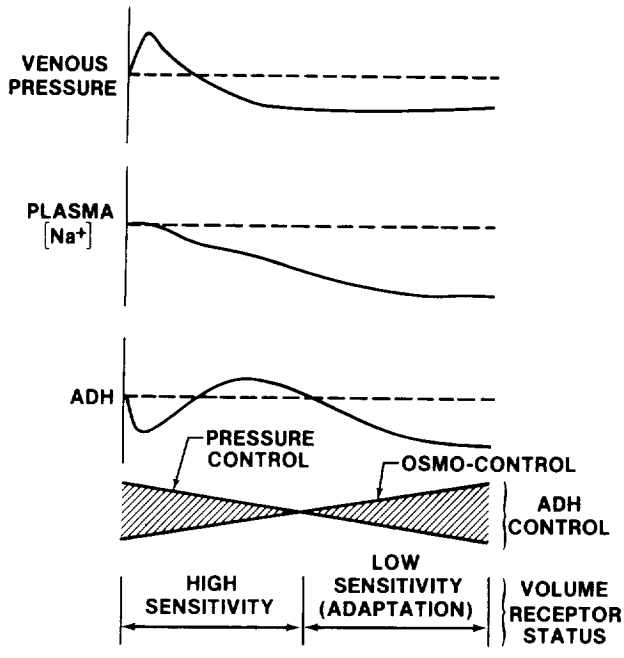


Figure 12. Hypothesis for ADH control during space flight

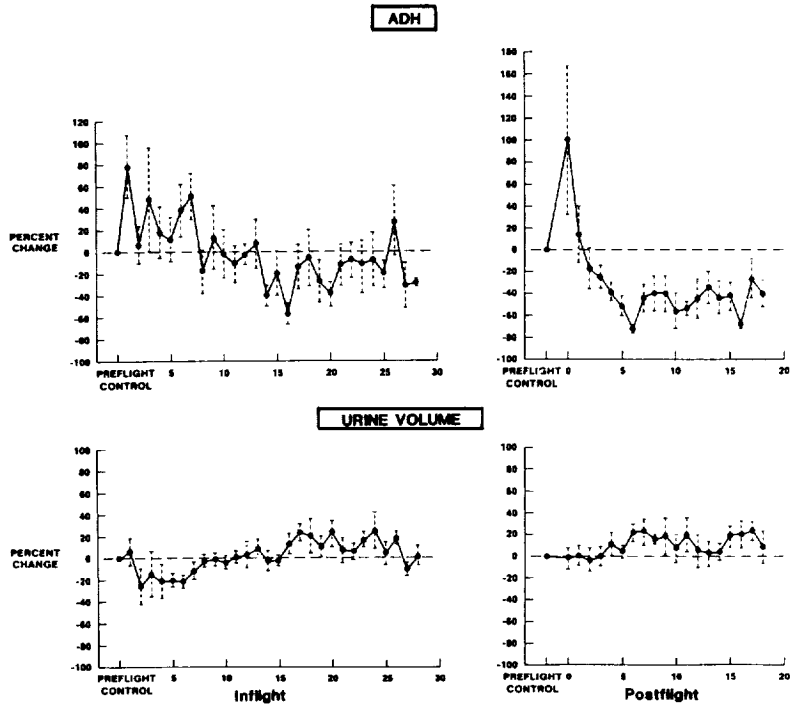


Figure 13. Urinary ADH and daily urine volume shown as percent change from preflight levels

percent (Ref. 31) which can be thought of as an effective increase in net fluid intake. As may be expected in such cases, urine output also increased a corresponding amount. Also, Figure 13 illustrates that on the average, ADH levels and urine volume are inversely related in zero-g, as one would expect from physiological theory in one-g. This has never been previously demonstrated.

These studies suggest a generalized theory that can explain the overall behavior of the major renal-regulating hormones. In particular, there appears to be a shift from short-term volume control to long-term metabolic control, especially resulting from chronic changes in electrolyte disturbances. While the acute affect generally leads to suppressed endocrine levels, the long-term effect can vary widely, depending on the particular combination of metabolic factors. These factors, such as diet, sweat loss, physical activity, and muscle atrophy, can alter the plasma electrolytes and thus influence hormone behavior. The analysis becomes complex because hormone changes then have a feedback effect on the electrolyte levels. Moreover, a transition between volume control and electrolyte control can produce a dynamic multi-phasic endocrine response. Within limits, we have shown that a mathematical model of this system is an effective tool with which to study many of these complex effects.

7. DISCUSSION

7.1 Future Work

Inasmuch as this research effort was concerned not only with specific mathematical models and simulation techniques, but also with the design and interpretation of physiological flight experiments it is natural to consider the future directions in both of these areas. With regard to the tools of modeling, it is clear that the modified Guyton model has served well in studying complex, whole-body phenomena concerned with circulatory and fluid regulation. However, it is also apparent that the model is limited; it does not contain sufficient detail to allow the simulation of certain physiological behavior. Since the publication of the Guyton model in 1972, there have been advances in several areas which should be considered for incorporation into the model. The current renal subsystem, for example, lacks some of the known intricacies regarding peritubular capillary effects, third factor effects, and factors influencing intrarenal blood flow. Also, acid-base balance and regulation is not represented in the current model. Similarly, modification of the Guyton model's hormone regulating pathways should reflect current knowledge in this area, especially with regard to relative sensitivities of competitive stimuli. Hormones such as natriuretic factor, prostaglandins and norepinephrine should be included in the next model generation. Finally, a more realistic approach to mathematically simulating hypogravity may involve changing the reference position of the model from the supine to the orthostatic position. This would provide an additional degree of freedom so that, for example, it would possible to more realistically distinguish between supine and head-down bed rest.

From an experimental viewpoint, it is possible to predict more rapid advances in data collection and hypothesis testing than has been witnessed in the past. No longer are observations limited only to pre- and postflight measurements, to non-invasive measurements, or to studies on only a few crewmembers. The most pressing need in the fluid-electrolyte discipline is the information related to acute changes. Virtually no data has been collected during the first few hours of weightlessness, when many of the responses discussed here may be transiently observed. Important aspects of an acute study should include confirmation of the expected headward volume shifts, the suppression and rebound of the renal-regulating hormones, the

existence of natriuretic factor, blood pressure disturbances, altered renal clearances, and the reduction in plasma volume. These are the type of short-term experiments that could ideally be conducted on the Shuttle and its Spacelab.

Studies of longer term adaptation, such as those conducted on a space station, could address such metabolic issues as the control of renal regulation, the etiology of hyponatremia, the factors leading to space flight anemia, the degree of long-term fluid congestion of the upper body, confirmation of sweat suppression, and the basis for increased systemic flow resistance. Other experiments are required to study the influence of diet as a potential countermeasure, shifts of circadian cycles, direct measurements of basal and work energy utilization, and potential metabolic changes at the microcirculatory and cellular levels. The role of hormonal regulators of renal functions during the chronic or adaptive phase of flight is not yet clearly defined. An assessment of renal function would be possible by performing renal stress tests in humans (fluid loading, salt loading, dehydration) and from studying glomeruli and turbular dynamics by renal micropuncture techniques in animals. Much of this information should be considered essential for defining a baseline norm for zero-g adaptation and health.

Several comprehensive experiments, on humans, primates, and rats have recently been selected for flight in answer to some of these research needs (Ref. 25). They will address fluid, electrolyte and circulatory issues including direct measurements of body fluids, venous pressure, renal regulating hormones, renal function, microcirculatory changes and circadian rhythms. A number of these studies resulted from the conclusions generated by the mathematical modeling analyses, some of which have been presented in this paper.

7.2 Conclusion

The findings and hypotheses discussed in this paper with regard to the fluid-electrolyte discipline have been integrated into a larger hypothesis of space-flight adaptation (Refs. 1, 6, 32, 33). All of the modeling studies conducted to date indicate that a significant portion of the known responses to weightlessness can be explained in terms of normal, although complex, feedback-regulatory processes. It appears however, that the feedback mechanisms that are known to explain the acute effects of space flight may not be capable of accounting for the longer term effects. In fact, little is known of the long-term adaptive mechanisms which occur in weightlessness and it is possible that models such as those used here can play an important role in suggesting testable hypotheses. In this context, models have proven to be least effective when used to merely predict a physiological outcome, but have been most effective when they are used to probe the behavior of the system and identify the critical questions.

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